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Blood and milk concentrations of metronidazole in mothers and infants

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1 Introduction

Metronidazole has become a commonly used antimicrobial agent in the treatment of puerperal infections. It is, however, generally recommended that women do not breast-feed during metronidazole therapy [1, 3, 8, 15] as a number of studies have demonstrated metronidazole in breast milk in concentrations which do not differ markedly from corresponding maternal blood levels [2, 7, 9, 14]. It has been stated [8] that isolated measurements of a drug in breast milk is of little significance and that both the mother and infant must be examined as drug absorption in the neonate may be limited or facilitated compared to the adult. Also, excretion and metabolism may be decreased in the neonate organism causing accumulation of the drug.

To our knowledge no studies have measured comparative levels of metronidazole in mothers and infants during therapeutic administration for puerperal infection in lactating mothers. We have performed such a study measuring the levels of metronidazole and its hydroxy metablite (I) in milk and blood of mothers and their suckling infants with a specific method. The object was to assess the amounts of the drug and its hydroxy-metabolite in the infant organism and their rates of clearance. We also analysed a series of simultaneous milk and blood samples in one mother and calculated milk/plasma and infant/mother plasma ratios.

Curriculum vitae

Graduation from the medical faculty, University of Copenhagen 1972. Internships in surgical gastroenterology, orthopedics, and gynecology & obstetrics at Gentofte Hospital 1972–78. Internal medicine at Bispebjerg Hospital 1976. Gynecology and obstetrics at Glostrup Hospital 1978–79. Gynecology and obstetrics as a senior registrar at Gentofte Hospital 1979–80. Gynecology and obstetrics as a senior registrar at Rigshospitalet, University of Copenhagen 1980–82. Specialist in gynecology and obstetrics 1981. Presently employed as a senior registrar in the department of gynecology at Bispebjerg Hospital, Copenhagen.

2 Material and method

Fifteen mothers in treatment for puerperal endometritis with metronidazole tablets consented to participate. Four of the patients received 400 mg and eleven 200 mg three times daily. All women received additional therapy, thirteen with pivampicillin tablets 350 mg and two with erythromycin tablets 500 mg three times daily. The medication was started from 0 to 22 days after parturition and all samples collected from at least 1 day after treatment start and up to 9 days after treatment start.

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Maternal blood samples were collected from two hours after intake of a tablet until next breast-feed irrespective of medication when a simultaneous blood and milk sample were taken. One mother had a series of synchronous blood and milk samples collected, i.e. at 10, 30, 60, 120, 180, and 240 minutes after medication.

At the time of milk sampling the infants were test weighed and 1 to 2 hours later they had a blood sample taken as peak plasma concentrations occur within 30 minutes to 3 hours after oral administration [4].

The analyses for metronidazole and its hydroxy metabolite (I) in milk and plasma were performed as a specific semi-micro high-pressure liquid chromatographic method as described by KAYE and co-workers [10]. The limit of sensitivity was less than 0.1 μg/ml.

3 Results

Concentrations of metronidazole and its hydroxy metabolite (I) in milk and in infant and maternal plasma are shown in Tabs. I and II. Mean and range for maternal and infant plasma levels and milk levels as well as milk/plasma ratios in mothers and infant/mother plasma ratios are shown in Tabs. III and IV for metronidazole and hydroxy metabolite (I).

Simultaneous milk and blood samples in one woman show almost identical levels of metronidazole and hydroxy metabolite (I) from 10 to 240 minutes after dosing (Tab. V).

Judging from milk levels the maximum dose of metronidazole ingested by one infant in one meal was 1.8 mg/100 mg and assuming a total daily intake of 500 ml and an average neonatal weight of 3.0 kg the amount taken would be 3.0 mg/kg/day.

The ratio between maternal and infant total clearance can be calculated, as $Cl_m = D_m \times F/C_m$, where Cl_m is total maternal clearance, D_m maternal dosage, F absorption fraction and C_m mean maternal plasma concentration and as $Cl_i = D_i \times F/C_i = V \times C_m \times M/P \times F/C_i$ where Cl_i is total infant clearance, D_i infant dosage, C_i mean infant plasma concentration, V milk volume ingested daily and M/P milk/plasma ratio which we equal 1 (Tab. III). The ratio is then $Cl_i/Cl_m = V \times C_m^2/(C_i \times D_m)$. With V = 500 ml the ratio is then 0.026 for D_m = 600 mg, C_m = 5.0 μg/ml and C_i = 0.8 μg/ml and 0.027 for D_m = 1200 mg,

Tab. I. Concentrations of metronidazole (M.) in μg/ml in mothers and infants. Time after dosing/feed in minutes.

Patient	M. mg/day	Mother								Infant	
		Plasma						Milk		Plasma	
		Time	Conc.	Time	Conc.	Time	Conc.	Time	Conc.	Time	Conc.
1	600	120	8.8	270	7.8			270	6.2	120	1.4
2	600	140	3.3	120	1.7			120	1.6	*)	–
3	1200	120	7.8	240	8.5	120	15.5	120	12.9	45	4.9
4	600	120	1.9	0	4.6	30	5.2	30	5.3	60	0.3
5	600	130	6.6	240	5.0			240	5.0	120	0.6
6	600 (twins)	120	4.5	240	3.5	120	5.7	120	5.5	60 60	0.6 0.5
7	600	120	8.3	240	7.9	120	11.6	120	12.2	60	0.6
8	600	120	1.0	240	1.0	150	3.8	150	4.4	60	0.7
9	600	120	3.4	30	5.6			30	7.0	60	1.1
10	600	120	4.2	240	4.2	180	5.5	180	5.8	60	1.0
11	600	105	5.0	240	3.9	60	6.1	60	3.8	60	0.4
12	1200	140	3.7	135	13.6			135	13.1	60	0.6
13	600	140	4.3	20	5.3			20	5.8	60	1.2
14	1200	120	13.5	180	11.7	240	9.6	180	11.6	120	2.3
15	1200	See Tab. V									

*) Sample too small to analyse

C_m = 12.5 μg/ml, and C_i = 2.4 μg/ml. If we assume infant and maternal weights to be 3.0 and 70.0 kg and body surfaces to be 0.2 m^2 and 1.8 m^2 infant clearance is 61 % and 63 % of maternal clearance by weight and 23 % and 24 % by body surface.

No adverse reactions were observed in mothers or infants.

4 Discussion

Breast-feeding involves benefits for the infant and its mother. Administration of drugs to the mother during the lactating period always raises the question of the possible harmful effects of the drug to the infant as virtually all drugs via the milk

Tab. II. Concentrations of hydroxy metabolite I in μg/ml in mothers and infants. Time after dosing/feed in minutes.

Patient	M. mg/day	Mother								Infant	
		Plasma						Milk		Plasma	
		Time	Conc.	Time	Conc.	Time	Conc.	Time	Conc.	Time	Conc.
1	600	120	3.4	270	4.0			270	3.0	120	0.8
2	600	140	1.7	120	1.7			120	1.9	*)	–
3	1200	120	1.7	240	1.8	120	2.4	120	2.8	45	2.3
4	600	120	1.2	0	1.2	30	1.5	30	2.0	60	0.2
5	600	130	1.2	240	1.2			240	1.4	120	n.d.
6	600 (twins)	120	1.8	240	1.9	120	1.9	120	2.4	60 60	0.5 0.5
7	600	120	2.6	240	2.8	120	3.1	120	3.8	60	0.4
8	600	120	0.9	240	0.8	150	0.9	150	1.3	60	0.2
9	600	120	1.1	30	1.4			30	1.9	60	0.5
10	600	120	1.5	240	1.7	180	1.9	180	2.1	60	0.6
11	600	105	1.0	240	1.3	60	1.6	60	1.1	60	0.2
12	1200	140	3.9	135	5.4			135	5.9	60	0.7
13	600	140	1.2	20	1.2			20	1.7	60	0.6
14	1200	120	4.9	180	5.3	240	5.5	180	6.3	120	1.1
15	1200	See Tab. V									

*) Sample too small to analyse.
n.d.: Not detectable, i.e. less than 0.1 μg/ml.

Tab. III. Concentrations of metronidazole in breast milk and infant and maternal plasma in μg/ml and milk/plasma and infant/mother plasma ratios.

Metronidazole mg/day	Number patients	Concentrations of metronidazole in					
		mothers				infants	
		plasma		milk		plasma	
		mean	range	mean	range	mean	range
600	11	5.0	1.0–11.6	5.7	1.6–12.2	0.8	0.3–1.4
1200	4	12.5	3.7–17.9	14.4	11.6–18.0	2.4	0.6–4.9

Metronidazole mg/day	Number patients	mothers milk/plasma		baby/mother plasma	
		mean	range	mean	range
600	11	0.99	0.62–1.25	0.13	0.05–0.23
1200	4	0.98	0.83–1.13	0.17	0.04–0.32

Tab. IV. Concentration of hydroxy metabolite (I) in breast milk and infant and maternal plasma in μg/ml and milk/plasma and infant/mother plasma rations.

Metronidazole mg/day	Number patients	Concentrations of hydroxy metabolite					
		mothers				infants	
		plasma		milk		plasma	
		mean	range	mean	range	mean	range
600	11	1.7	0.8–4.0	2.1	1.1–3.8	0.4	0.1–0.8
1200	4	3.2	1.7–5.5	3.5	2.4–6.3	1.1	0.4–2.3

Metronidazole mg/day	Number patients	mothers milk/plasma		baby/mother plasma	
		mean	range	mean	range
600	11	1.17	0.69–1.44	0.23	0.08–0.50
1200	4	1.20	1.04–1.35	0.37	0.13–0.96

reach the infant organism. The safety evaluation of metronidazole is based mainly on animal studies and clinical experience derived from the adult population [5, 13]. Absorption of metronidazole in neonates may be altered and as metronidazole is primarily excreted by the kidneys, the newborn may accumulate the drug resulting in higher concentrations than in the adult organism. Studies [2, 7, 9, 14] dealing with metronidazole administration to lactating women involve only few infants and only one study besides the present has analysed infant blood levels.

GRAY and co-workers' [9] study involved 10 mothers who were given a single tablet of 200 mg metronidazole. Mean concentrations in breast milk varied between 1.3 and 3.4 μg/ml and between 1.8 and 3.9 μg/ml in serum. Blood tests from 5 babies contained no detectable metronidazole and in 5, levels ranged from 0.05 to 0.4 μg/ml. The maximum amount ingested by one infant calculated from test weighings was 0.41 mg. As expected these figures all range below our findings which are based on the therapeutic administration of metronidazole to the mothers.

AMON et al. [2] examined 6 puerperae who were given 250 mg metronidazole orally twice daily. The highest level in breast milk was found to be 6.8 μg/ml and the maximum amount actually taken by the newborn was 0.17 mg/kg/100 ml milk which is about one third of the amount we have estimated. The coefficient of distribution milk: Serum was below 1.0 in four and above 1.0 in two mothers which compares well with our milk/plasma ratios.

The administration of metronidazole in the Study Group [14] report is the only one comparable to a

Tab. V. Simultaneous maternal milk and plasma concentrations in μg/ml of metronidazole and hydroxy metabolite (I) in one mother receiving 1200 mg metronidazole daily.

		Time in minutes after medication					
		10	30	60	120	180	240
Metronidazole	Plasma	11.7	12.2	15.4	17.8	17.9	16.3
	Milk	13.2	13.4	13.2	18.0	17.6	16.3
Hydroxy met.	Plasma	1.9	2.0	2.2	2.3	2.5	2.4
	Milk	2.5	2.7	2.4	3.0	2.6	3.0

clinical administration of the drug, i.e. 200 mg oral metronidazole at eight-hourly intervals. Milk samples from mothers contained a mean of 4.7 (range 1.1–15.2) μg/ml and blood a mean of 7.8 (range 2.0–14.6) μg/ml. These findings are in accordance with the ones in the present study, where the range too is almost 10-fold. The variation in our study was seen between mothers as samples from the same mother showed less variations (Tab. I). This inter-maternal variation is probably due to differences in body weight and intestinal absorption.

ERICKSON et al. [7] measured metronidazole concentrations in breast milk from 3 women who had been treated with a single 2 gram dose. Estimated consumption based on 1,000 mg breast milk intake by a baby was 21.8 mg during the first 24 hours.

No pharmacokinetic studies of metronidazole have involved neonates why the intestinal absorption is unknown. Assuming that the mean maternal and infant plasma levels represent steady state concentrations we calculated the infant total clearance to be around 60% by weight and around 24% by body surface of the maternal clearance. This finding is in good accordance with the clearance ratios found for other antimicrobial chemotherapeutics such as gentamycin [12]. The fraction is apparently independent of the daily intake. The maximum intake by an infant in our study was calulated to be 3.0 mg/kg with 500 ml milk intake per day which is well below the advocated 10–20 mg/kg metronidazole dosage in the treatment of infants. On the other hand, **a 1200 mg daily intake of metronidazole by the mother may result in almost therapeutic levels in infants.**

The hydroxy metabolite (I) like the parent compound is known to possess antimicrobial and mutagenic activity. The antimicrobial activity of the metabolite tested on clostridial species was found to be 30% of metronidazole [6] whereas the mutagenic activity tested in vitro with Salmonella Typhimurium was found to be 10 times higher [11]. The significance of these findings in humans is unknown. In all instances we found the levels of the hydroxy metabolite (I) to be considerably lower than those of metronidazole.

Our conclusion is that infants do receive metronidazole via breast milk in considerable doses and attain measurable levels in their organisms. On these grounds, it seems wise to prescribe metronidazole with caution to lactating women. The ultimate decision whether to stop or continue breastfeeding during metronidazole therapy still has to be based on our insufficient knowledge of the possible long-term harmful effects of the drug on the neonate, as only few and mild instant adverse reactions are seen.

Summary

In order to assess the amounts of metronidazole and its clearance in suckling neonates whose mothers received the drug in therapeutic doses, we measured its levels in maternal plasma and milk and in infant plasma. **Eleven mothers receiving 600 mg metronidazole daily and 4 receiving 1200 mg and their 15 infants had milk and plasma levels determined** with a specific semi-micro high-pressure liquid chromatographic method. Maternal mean plasma levels were 5.0 μg/ml, range 1.0–11.6 μg/ml (600 mg/day) and 12.5 μg/ml range 3.7–17.9 μg/ml (1200 mg/day) and corresponding infant plasma levels were 0.8 μg/ml, range 0.3–1.4 μg/ml and 2.4 μg/ml, range 0.6–4.9 μg/ml. Maternal milk/plasma ratio was 1 and baby/mother plasma ratio was 0.15, independent of dosage (Tab. I). The levels of metronidazole hydroxy metabolite (I) were all below those of metronidazole (Tab. II). Simultaneous milk and blood samples showed almost identical levels (Tab. III).

Infant total clearance of metronidazole was calculated to be ca. 60% of maternal clearance by body weight and 24% by body surface, independent of dosage, while maximum infant metronidazole intake was estimated to be 3.0 mg/kg/day assuming a daily intake of 500 ml milk. **It is recommended to avoid simultaneous breastfeeding and metronidazole therapy until possible harmful longterm effects on the neonates are known.**

Keywords: Infant clearance, infant plasma levels, lactation, metronidazole.

Zusammenfassung

Metronidazolplasmaspiegel bei Müttern und ihren Neugeborenen und Konzentration in der Brustmilch
Ziel unserer Untersuchung war die Ermittlung der Metronidazol-Konzentration bzw. -Clearance bei gestillten Neugeborenen, deren Mütter mit diesem Medikament in therapeutischen Dosen behandelt wurden. Dazu bestimmten wir die Plasmaspiegel bei Mutter und Kind sowie die Konzentration in der Brustmilch. **11 Mütter erhielten 600 mg Metronidazol pro Tag und 4 Mütter 1200 mg pro Tag.** Die Konzentrationen wurden mit einer spezifischen Methode, der Hochdruckflüssigkeitschromatographie, ermittelt. Bei den Frauen, die 600 mg/d erhielten, lagen die Plasmaspiegel zwischen 1.0 und 11.6 µg/ml, also durchschnittlich 5.0 µg/ml; Mütter, die 1200 mg/d erhielten, wiesen Plasmaspiegel zwischen 3.7 und 17.9 µg/ml, d.h. durchschnittlich 12.5 µg/ml auf. Bei den Neugeborenen wurden bei der geringeren Tagesdosis mittlere Spiegel von 0.8 µg/ml (0.3–1.4 µg/ml) bestimmt, bei der doppelten Dosis lag er bei durchschnittlich 2.4 µg/ml (0.6–4.9 µg/ml). Das Verhältnis zwischen mütterlichem Plasmaspiegel und Brustmilch betrug 1, das Verhältnis von kindlichem zu mütterlichem Plasmaspiegel lag unabhängig von der Dosis bei 0.15 (Tab. I). Die Konzentration der Metaboliten lag in jedem Fall unter der von Metronidazol (Tab. II). Die gleichzeitige Bestimmung in Milch- und Plasmaproben ergab fast immer identische Spiegel (Tab. III). Die totale Metronidazol-Clearance beim Kind berechnete sich zu 60% der mütterlichen Clearance durch das Körpergewicht und zu 24% durch die Körperoberfläche. Sie zeigte sich unabhängig von der Dosierung. Die maximale Metronidazolaufnahme durch das Kind wurde auf 3.0 mg/kg/d geschätzt, wenn man eine tägliche Trinkmenge von 500 ml Milch ansetzt. **Wir empfehlen, unter Metronidazoltherapie mit dem Stillen aufzuhören, da schädigende Wirkungen auf das Neugeborene nicht ausgeschlossen werden können.**

Schlüsselwörter: Clearance beim Kind, Laktation, Metronidazol, Plasmaspiegel beim Kind.

Résumé

Concentration de métronidazole dans le sang et dans le lait chez les mères et les enfants
Les auteurs ont mesuré les taux de métronidazole dans le plasma maternel et le lait ainsi que dans le plasma des enfants, afin de déterminer les quantités de métronidazole et sa clearance chez les nouveaux-nés nourris au sein dont les mères reçoivent ce produit à doses thérapeutiques. Les taux plasmatiques et du lait ont été mesurés à l'aide d'une semi-micro méthode specifique par chromatographie avec liquide à haute pression, chez **11 mères recevant 600 mg de métronidazole par jour et chez 4 recevant 1200 mg de métronidazole par jour ainsi que chez leurs 15 enfants.** La moyenne des taux plasmatiques maternels est de 5 µg/ml, avec des écarts compris entre 1 et 11,6 µg/ml (600 mg/ jour) et 12,5 µg/ml avec des écarts allant de 3,7 à 17,9 µg/ml (1200 mg/jour), tandis que les taux plasmatiques correspondants des enfants sont de 0,8 µg/ml, avec des écarts de 0,3 à 1,4 µg/ml et 2,4 µg/ml, avec des écarts de 0,6 à 4,9 µg/ml. Le rapport lait maternel/plasma est de 1 et le rapport plasmatique enfant/mère est de 0,15, indépendamment des dosages (Tab. I). Les taux de métabolite hydroxylé du métronidazole (I) sont tous en-dessous de ceux du métronidazole (Tab. II). Les échantillons simultanés de lait et de sang montrent des taux à peu près identiques (Tab. III).
La clearance totale du métronidazole chez l'enfant a été déterminée à 60% de la clearance maternelle en fonction du poids corporel, et à 24% en fonction de la surface corporelle sans lien avec la posologie, alors que l'apport maximum de métronidazole chez l'enfant a été estimé à 3 mg/Kg/jour, ce qui correspond à une quantité journalière de 500 ml de lait.
Il est recommandé d'éviter l'allaitement au sein lors des traitements par métronidazole, tant qu'un éventuel effet nocif à long terme chez le nouveau-né n'aura pas été éliminé.

Mots-clés: Allaitement, clearance chez l'enfant, metronidazole, taux plasmatique de l'enfant.

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